

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO			
RAD: 11-149811- -7	FECHA: 2013-06-20 09:14:11		
DEP: 2020 DIRECCION DE NUEVAS CREACIONES	EVE: 378 FASE NACIONAL INCLUIDO CAPITULO I		
TRA: 11 PCT-PATENTE DE INVENCION CAPITULOS I Y II	FOLIOS: 5		
ACT: 519 PRESENTACION			

DIRECCIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado(a)/Señor(a)
LUZ CLEMENCIA SUAREZ DE PAEZ

Asunto: Radicación: 11-149811- -7
Trámite: 11
Evento: 378
Actuación: 519
Oficio: 10684
Folios: 5

Patente de Invención	X			Patente de Modelo de Utilidad	
Vía Nacional					
Vía PCT (Fase Nacional)	X	Capítulo I	X	Capítulo II	
No. Solicitud Internacional	PCT//FR2010/050873				
Fecha de Presentación Internacional	06/05/2010				

Como resultado del examen de fondo realizado, con fundamento en el Artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

1. Documentos estudiados

Descripción:	Radicado No 11-149811-00000-0000	04/Noviembre/2011
Reivindicaciones:	1 – 11 del radicado No 11-149811-00000-0000	04/Noviembre/2011
Oposiciones:	Radicado No 11-149811-00001-0000	Synthesis S.A.S. 14/mayo/2012
Oposiciones:	Radicado No 11-149811-00002-0000	Lafrancol 30/mayo/2012
Respuesta solicitante del	Radicado No 11-149811-00006-0000	22/Octubre/2012
Prioridad:	FR 0902189	06/Mayo/2009
	FR 0902264	11/Mayo/2009

2. Análisis de la Prioridad

Se acepta la reivindicación de prioridad porque ésta solicitud fue presentada dentro del plazo establecido (Art. 9 D 486) y su contenido técnico corresponde con el de la prioridad reivindicada.

3. Objeto de la invención

De acuerdo con lo establecido en el numeral 1.2.2.2 del Capítulo Primero del Título X de la Circular Única para efectos del examen de patentabilidad, se tendrá en cuenta la tasa pagada por el solicitante al momento de comenzar el examen para las reivindicaciones adicionales; esto es que cuando la solicitud contenga más de diez (10) reivindicaciones y no se haya pagado la tasa complementaria, sólo se estudiarán las cubiertas por la tasa pagada.

Dado que en la presente solicitud se evidencia pago de tasa por reivindicación adicional se procede a estudiar las 11 reivindicaciones del capítulo reivindicatorio.

Título de la solicitud: “Combinación antitumoral que comprende cabazitaxel y capecitabina”.

El problema planteado en esta solicitud consiste en proporcionar una combinación antitumoral adecuada para el tratamiento del cáncer de mama metastásico en pacientes que progresan después de un tratamiento anterior con antraciclinas y taxanos.

Para resolver este problema técnico la solicitud en estudio proporciona una combinación de cabazitaxel y capecitabina.

El objeto de la presente solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): A61K 31/337.

4. Excepción a la Patentabilidad (Art 20 D 486 literales (a) – (d))

El objeto de las reivindicaciones 5 – 10, que se refieren a métodos de tratamiento, no es patentable de acuerdo con el Art citado.

Es importante aclarar a la solicitante, que si bien las reivindicaciones se encabezan como “combinación”, en las mismas se definen las dosis (para cada administración), la vía de administración, el tiempo de duración, así como las instrucciones a seguir, lo que corresponde a un claro método de tratamiento.

5. Reivindicaciones relativas a un uso o a un segundo uso (Art 14 y 21 D 486)

El uso de la reivindicación 11 no es patentable, de acuerdo con el Art 14.

6. De la solicitud de patente

Reivindicaciones (Art 30 D 486, Art 22 PCT)

La Reivindicación 1 no es clara porque la combinación farmacéutica que se pretende reclamar no menciona las cantidades del principio activo que la diferencian del arte previo. Se sugiere definir la combinación por sus componentes específicos y las cantidades de cada uno de los mismos.

Lo anterior aplica para las reivindicaciones 2 – 4.

La reivindicación 3 no es clara cuando menciona “solvato” acetónico, ya que esta definición corresponde a un pseudopolimorfo y tal como se encuentra contemplado no es claro porque no caracteriza apropiadamente el cristal reivindicado debido a que no presentan por lo menos los 20 picos correspondientes a las intensidades de los haces difractados o a los espacios interplanares d_{hkl} según los índices de Miller (hkl) medidos de acuerdo con el ángulo de difracción de Bragg 2θ en el intervalo más representativo comprendido entre 5° hasta 90° . Se sugiere eliminarla del pliego reivindicatorio. Lo anterior aplica para la Reivindicación 4.

7. Análisis de las Oposiciones

Argumentaciones de Synthesis S.A.S.

El Opositor argumenta que la presente solicitud de patente no cumple con los requisitos de patentabilidad, tales como nivel inventivo y aplicación industrial, que además en la solicitud se encuentran reivindicaciones que se refieren a métodos de tratamiento y usos de la combinación, y que antes de la fecha de prioridad de esta solicitud se encontraba el siguiente documento que afecta la patentabilidad de la presente solicitud:

- **D1:** PIVOT X ET AL: "A multicenter phase II study of XRP6258 administered as a 1-h i.v. infusion every 3 weeks in taxane-resistant metastatic breast cancer patients." ANNALS OF ONCOLOGY: OFFICIAL JOURNAL OF THE EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY / ESMO SEP 2008, vol. 19, no. 9, September 2008 (2008-09).

El Opositor señala que a partir de D1 es posible determinar que en pacientes con cáncer de mama el uso de cabazitaxel y capecitabina en combinación son bien tolerados y que estabilizan la enfermedad en un 60%, además que cabazitaxel y capecitabina son eficaces en tratamiento de cáncer de mama metastásico resistente a docetaxel o paclitaxel con una tasa de respuesta del 14% para cabazitaxel y capecitabina en un 20%. Por lo anterior, el Opositor señala que el problema que pretende resolver la presente invención no comprende nivel inventivo pues no se está definiendo una fórmula mejorada sobre el arte conocido.

Argumentaciones de Lafrancol

El Opositor afirma que la presente solicitud incumple con los requisitos materiales de Patentabilidad, particularmente Novedad y Nivel Inventivo. El Opositor señala que composiciones y combinaciones farmacéuticas que comprenden Cabazitaxel y Capecitabina, que se usan en el tratamiento de cáncer metastásico de mama después de un tratamiento anterior con antraciclinas y taxanos, son prácticas totalmente conocidas en la industria farmacéutica. El Opositor también señala, en cuanto a las composiciones farmacéuticas, que no se puede otorgar el beneficio patentario a composiciones farmacéuticas que comprenden moléculas que se encuentran

descubiertas y plenamente identificadas en el sector químico-farmacéutico. El Opositor señala que así es como en “The Merck Index” se enseña que la Capecitabina se encuentra plenamente identificada y bajo conocimiento público desde un tiempo considerable. Adicionalmente, el Opositor argumenta que la Capecitabina también se encuentra plenamente identificada y bajo el conocimiento público desde hace un tiempo muy considerable y además ostenta beneficios patentarios concedidos por Estados Unidos con No. **EP 602454 y US5472949** y que el Cabazitaxel se encuentra plenamente identificada tanto en la literatura médico científica como en el estado del arte. El Opositor concluye que no se puede conceder una patente a composiciones y combinaciones farmacéuticas que contienen moléculas plenamente identificadas y conocidas, pues no son nuevas ni inventivas y que la “combinación” de productos conocidos no se consideran susceptibles de aplicación industrial, nivel inventivo y novedad.

Respuestas del Solicitante

- Respuesta a las oposiciones de Synthesis S.A.S. y Lafrancol S.A.

Como respuesta a los argumentos de Lafrancol la solicitante menciona que tales consideraciones respecto a la novedad y nivel inventivo no son adecuadas frente a la metodología que debe adelantarse para determinar la patentabilidad de una solicitud de patente, ya que no se señala el documento considerado del estado del arte cercano a la invención que pueda afectar su patentabilidad sino que simplemente se dedica a enumerar unos documentos con los cuales no objeta adecuadamente la invención, esto es, a señalar con un documento que explícitamente señale todas las características técnicas de la invención y/o que revele sugerencias y enseñanzas claras para el técnico en la materia. Dado que el Opositor no cumple con lo anteriormente expuesto, la solicitante considera infundada la oposición.

Ahora, como respuesta a los argumentos de Synthesis S.A.S. y frente al documento D1 por esta sociedad opositora citado la solicitante considera que esta referencia no enseña ni sugiere la combinación de cabazitaxel con capecitabina, afirma que aún con el conocimiento de que cada uno de los compuestos es utilizado en el tratamiento de cáncer de mama, no resulta obvia su combinación. Además señala la solicitante que la presente invención tiene un efecto inesperado dado por la dosis de cada fármaco y el esquema de administración conveniente, no exacerbando la toxicidad de cada uno de los mismos.

Respuesta del Examinador Técnico

En respuesta a los argumentos presentados por las sociedades opositoras Lafrancol, Synthesis y la respuesta de la solicitante, se encuentra que:

Efectivamente le asiste la razón a la sociedad Synthesis en cuanto a que el documento D1 afecta la patentabilidad de la presente invención por sus enseñanzas, y por tanto será considerado dentro del examen de patentabilidad.

Ahora, en cuanto a los argumentos de la sociedad Lafrancol, si bien es cierto que las moléculas cabazitaxel y capecitabina, están plenamente identificadas en el campo químico-farmacéutico, en “The Merck Index”, en las patentes concedidas por Estados Unidos y en la literatura médico científica, no se están presentando documentos que divulguen o sugieran la combinación de estos dos principios activos, por lo tanto, estas referencias y argumentos no serán considerados para el análisis de patentabilidad.

8. Determinación del Estado de la Técnica

El estado de la técnica se determinó con base en la fecha de presentación de la solicitud de la cual se invoca prioridad, es decir, el 06 de mayo de 2009.

Consultadas las fuentes de información con que se cuenta, se encontró (encontraron) el (los) siguiente (s) documento (s) que anticipa (n) el objeto de esta solicitud:

Ítem	Documento	Título	Fecha de Publicación*
D1	artículo	"multicenter phase II study of XRP6258 administered as a 1-h i.v. infusion every 3 weeks in taxane-resistant metastatic breast cancer patients"	Septiembre/2008
D2	artículo	"Impact, mechanisms, and novel chemotherapy strategies for overcoming resistance to anthracyclines and taxanes in metastatic breast cancer"	Marzo/2009

El documento D1 ¹ (todo el documento) divulga el uso de XRP6258 (Cabazitaxel) un novedoso taxoide con baja actividad por la glicoproteína P, como agente utilizado en pacientes con cáncer de mama metastásico resistente a taxanos.

El documento D2 ² (pág. 195 en resumen e introducción) diferentes mecanismos y estrategias quimioterapéuticas para afrontar los problemas de resistencia a las antraciclinas y los taxanos en cáncer de mama metastásico.

El documento D3 ³ (pág. 195 en resumen e introducción) diferentes mecanismos y estrategias quimioterapéuticas para afrontar los problemas de resistencia a las antraciclinas y los taxanos en cáncer de mama metastásico

9. Examen de Patentabilidad (Art 14 D486)

Nivel inventivo (Art18 D486)

La reivindicación 1 consiste en una combinación farmacéutica antitumoral que comprende cabazitaxel y capecitabina... (Ver pág. 14 del radicado No 11-149811-00000-0000).

Comparación de las características técnicas esenciales, con las del estado de la técnica:

Características esenciales	D1	D2
Combinación farmacéutica	No menciona	Combinación para quimioterapia (pág. 196, tabla 1)

1 **PIVOT X ET AL**: "A multicenter phase II study of XRP6258 administered as a 1-h i.v. infusion every 3 weeks in taxane-resistant metastatic breast cancer patients." ANNALS OF ONCOLOGY: OFFICIAL JOURNAL OF THE EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY / ESMO SEP 2008, vol. 19, no. 9, September 2008 (2008-09), pages 1547-1552,
 URL: <http://annonc.oxfordjournals.org/content/19/9/1547.full.pdf+html>

2 **PEREZ E A**: "Impact, mechanisms, and novel chemotherapy strategies for overcoming resistance to anthracyclines and taxanes in metastatic breast cancer" BREAST CANCER RESEARCH AND TREATMENT 200903 US, vol. 114, no. 2, mars 2009 (2009-03), pages 195-201,
 URL: <http://link.springer.com/article/10.1007%2Fs10549-008-0005-6>

3 **PEREZ E A**: "Impact, mechanisms, and novel chemotherapy strategies for overcoming resistance to anthracyclines and taxanes in metastatic breast cancer" BREAST CANCER RESEARCH AND TREATMENT 200903 US, vol. 114, no. 2, mars 2009 (2009-03), pages 195-201,
 URL: <http://link.springer.com/article/10.1007%2Fs10549-008-0005-6>

Cabazitaxel	Cabazitaxel (todo el documento)	No menciona particularmente cabazitaxel pero divulga el análogo estructural docetaxel (compuesto de la familia de los taxoides).
Capecitabina	Capecitabina (pág. 1551, “discussion”)	Capecitabina (pág. 196, tabla 1)

Los documentos D1 y D2 se consideran el estado de la técnica cercano a la invención definida en la reivindicación 1 porque divulga el uso de XRP6258 (Cabazitaxel), un novedoso taxoide con baja actividad por la glicoproteína P, como agente utilizado en pacientes con cáncer de mama metastásico resistente a taxanos y diferentes mecanismos y estrategias quimioterapéuticas para afrontar los problemas de resistencia a las antraciclinas y los taxanos en cáncer de mama metastásico. (D2: pág. 195 en resumen e introducción).

La diferencia entre la invención, definida en la reivindicación 1 y el documento D1 consiste en que particularmente no aclara una combinación farmacéutica que comprenda cabazitaxel con capecitabina.

La diferencia entre la invención, definida en la reivindicación 1 y el documento D2 consiste en la presencia de cabazitaxel en la combinación con capecitabina.

La presencia de Cabazitaxel no parece conceder un efecto técnico inesperado o una ventaja a la combinación reclamada en esta solicitud ya que no parecen presentar propiedades superiores en comparación con las combinaciones del estado de la técnica cercano.

Por lo tanto, el problema técnico objetivo que pretende resolver esta invención se puede formular como la necesidad de una combinación, particularmente un porfármaco de 5-fluorouracilo tal como Capecitabina y un compuesto de la familia de los taxoides, tal como cabazitaxel, como agentes contra cáncer de mama metastásico, principalmente para los pacientes que escapan de un tratamiento basado en antraciclinas y/o taxanos.

Sin embargo, D2 ya sugería una combinación terapéutica de Capecitabina con un compuesto tipo taxoide, D2 particularmente señala (pág. 196, tabla 1) la combinación de capecitabina con docetaxel (compuesto de la familia de los taxoides).

En consecuencia, la persona del oficio normalmente versada en la materia en vista de las enseñanzas de D2 habría podido modificar el compuesto de la familia de los taxoides, en particular con el compuesto cabazitaxel revelado en D1 para llegar así al objeto de la reivindicación 1 de la solicitud. Por lo cual se considera obvia.

Puesto que las reivindicaciones dependientes 2 – 4 no mencionan características inventivas adicionales tampoco se pueden considerar inventivas

10. Conclusión

Los requisitos de Patentabilidad de la presente solicitud están afectados así:

Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	PIVOT X ET AL	1 – 4	Nivel inventivo
D2	PEREZ E A	1 – 4	Nivel inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta (60) días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Se invita al solicitante se sirva indicar, si así lo considera, su renuncia al término faltante de sesenta (60) días para dar respuesta a este requerimiento y presentarla por escrito.

Finalmente, se le recuerda al solicitante que si como respuesta a este requerimiento llegara a modificar el capítulo reivindicatorio y éste contenga más de diez (10) reivindicaciones, no pagará la tasa de modificación voluntaria pero sí la correspondiente al pago por reivindicación adicional.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No. 10 de 2001.



JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista, de fecha 2013-06-25

Elaboró: Nelson Ricardo Velasco Gonzalez
Revisó: Gloria Jacqueline Alfonso Rozo

A multicenter phase II study of XRP6258 administered as a 1-h i.v. infusion every 3 weeks in taxane-resistant metastatic breast cancer patients

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Received 14 February 2008; revised 19 March 2008; accepted 20 March 2008

Background: XRP6258 is a novel taxoid with a low affinity for P-glycoprotein. This multicenter phase II study assessed the activity of XRP6258 in the treatment of taxane-resistant metastatic breast cancer (MBC).

Patients and methods: XRP6258 was administered as a 1-h i.v. infusion every 3 weeks at 20 mg/m² (then, in the absence of severe toxicity, at 25 mg/m² from cycle 2). The primary end point was the objective response rate (ORR) assessed according to response evaluation criteria in solid tumours (RECIST) guidelines.

Results: Seventy-one patients were enrolled. The median relative dose intensity was 0.98. The ORR was 14% (two complete, eight partial responses). Eighteen patients (25%) had stable disease of >3 months duration. At a median follow-up of 20.0 months, the median time to progression was 2.7 months, and the median overall survival 12.3 months. The most common grade 3/4 adverse events (AEs) were neutropenia (73%) and leucopenia (55%), with a low febrile neutropenia rate (3%) and infrequent grade 3/4, treatment-related, non-hematological AEs (<5% patients for any AE). Two deaths were reported, one related to study drug and one to unknown cause.

Conclusions: XRP6258 was active and well tolerated in this group of MBC patients with taxane-resistant disease. These results support the further clinical development of this agent.

Key words: chemotherapy, metastatic breast cancer, resistance, taxane, taxoid, XRP6258

introduction

While breast cancer is generally not overtly metastatic at presentation (~6% cases), ~30% of women with early stage lesions eventually develop advanced disease [1]. Metastatic breast cancer (MBC) remains essentially incurable, with median survival in the range of 2–4 years [2]. In this clinical situation, systemic therapies are palliative, aiming primarily at controlling disease symptoms, improving survival and preserving quality of life [3]. Regimens containing anthracyclines and taxanes as first-line treatment in MBC have demonstrated their potential to prolong patient survival [1, 4, 5]. When disease progression occurs after the completion of first-line treatment, additional lines of chemotherapy may be administered, with the capecitabine–docetaxel combination being an important treatment option for women with anthracycline-pretreated MBC [6, 7]. However, if metastatic disease becomes resistant to anthracycline and/or taxanes,

effective treatment options are limited. With the growing use of anthracycline/taxane-containing regimens in adjuvant therapy, there remains an unmet clinical need for effective compounds to treat patients with MBC developing or having developed resistance to taxanes.

For this reason, a program of medicinal chemistry was undertaken to identify new taxoid compounds with a broader spectrum of activity than the marketed taxanes, paclitaxel and docetaxel. XRP6258 and larotaxel (XRP9881) are new taxoids efficient in stabilizing microtubules against cold-induced depolymerization, the mechanism of action which is unique to the taxane class [8]. While the commercially available taxanes are substrates for P-glycoprotein, encoded by the multidrug resistance gene *ABCB1*, XRP6258 and larotaxel were selected for their low affinity for this drug efflux pump [9, 10]. This optimization suggested that both could be clinically effective in tumors expressing a multidrug resistance phenotype as a consequence of high-level expression of P-glycoprotein. Preclinical studies demonstrated that XRP6258 was cytotoxic for cell lines with acquired resistance to doxorubicin, vincristine, vinblastine, paclitaxel or docetaxel

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[11]. Similarly, both agents showed an *in vivo* spectrum of antitumor efficacy on most docetaxel-sensitive, -refractory or -resistant models, such as B16/TXT melanoma [9, 11]. Interestingly, both compounds showed the ability to cross the blood–brain barrier, a characteristic which may be a consequence of their low affinity for P-glycoprotein [12, 13].

Weekly and every 3-week schedules of administration of XRP6258 were tested in phase I trials [14, 15]. In one study, XRP6258 was given on a weekly schedule as a 1-h i.v. infusion on days 1, 8, 15 and 22 every 5 weeks. For the weekly regimen, the recommended dose was 10 mg/m² and the dose-limiting toxicity was diarrhea. Two studies have been carried out with XRP6258 administered as a 1-h i.v. infusion every 3 weeks. For this regimen, the maximum tolerated dose (MTD) was reached at the 30 mg/m² dose level, at which dose-limiting adverse events (AEs) such as febrile neutropenia and grade 4 neutropenia >5 days occurred. The recommended dose for phase II and III studies was 20 mg/m².

Originally, a three-arm study was initiated which was designed to compare the relative efficacy and safety of the two new taxoids, XRP6258 and larotaxel. However, due to low recruitment during the first 6 months, the protocol was amended to a single-arm phase II study exploring the activity of XRP6258 given every 3 weeks in patients with taxane-resistant MBC, as summarized in Figure 1. Consequently, only the data from this arm are reported.

patients and methods

This open-label phase II study was conducted in 39 study centers in Europe, Northern America and Southern America from August 2002 to January 2005 (cut-off date). The protocol complied with recommendations of the 18th World Health Congress (Helsinki, 1964) and all relevant amendments and was approved by the ethics committee of each participating institution. All patients gave their written informed consent.

main eligibility criteria

Eligibility criteria included the following: age ≥18 years, with histologically confirmed human epidermal growth factor receptor 2 (HER2)-negative (or HER2-positive previously failing trastuzumab) metastatic breast adenocarcinoma, Eastern Cooperative Oncology Group performance status (PS) zero to two and adequate hematological (granulocytes ≥2 × 10⁹/l, platelet count ≥100 × 10⁹/l), renal [creatinine ≤upper limit of normal (ULN) or creatinine clearance ≥60 ml/min] and liver (total bilirubin ≤ULN,

serum aspartate aminotransferase/alanine aminotransferase and alkaline phosphatase ≤2.5 × ULN) functions. Patients were required to have at least one measurable lesion according to RECIST guidelines [16].

Resistance to previous taxane-containing chemotherapy was required. This resistance was defined as: for advanced disease; progressive disease (PD) as the best overall response after first- or second-line treatment; or, PD within 4 months following discontinuation of first- or second-line treatment after an initial objective response or disease stabilization; or, stable disease (SD) as the best overall response if first- or second-line treatment with a taxane-containing regimen had been administered for at least 3 months; or, for patients who had received an adjuvant or neo-adjuvant taxane-containing regimen, a disease-free interval (DFI) ≤12 months from the end of treatment.

Patients were excluded if they had concurrent cancer, received more than two lines of chemotherapy for metastatic disease, hypercalcemia, grade 2 or 3 neuropathy, brain or leptomeningeal symptomatic involvement or uncontrolled significant comorbid conditions.

treatment assignment and schedule

Patients in the analyzed experimental arm received XRP6258 at 20 mg/m², given as a 1-h i.v. infusion on day 1 every 3 weeks. Inpatient dose escalation to 25 mg/m² was permitted in patients who did not experience a significant AE during cycle 1. Patients received i.v. antihistaminic anti-H1 premedication 30 min before study drug administration. No prophylactic antiemetic drugs were allowed at the first cycle. In case of nausea/vomiting, patients could receive preventive antiemetic treatment in compliance with the conventional antiemetic protocol of the center, for subsequent cycles. In the event of a treatment-related severe AE occurring during any cycle, a 20%–25% dose reduction and treatment delay for the individual drug was required on the basis of predefined criteria. Treatment was continued until disease progression, the occurrence of an unacceptable AE or the withdrawal of patient consent.

evaluations before and during therapy

Before registration, a complete medical history was taken and a physical examination was carried out, which included a complete blood count, blood chemistry analyses and tumor assessments.

Tumor measurements were made every 6 weeks by chest, abdominal and brain computed tomography scans or magnetic resonance imaging. Responses had to be confirmed by two evaluations taken at least 4 weeks apart. Complete blood counts were routinely carried out weekly or every day if grade 4 neutropenia occurred (until recovery to grade 3) or in the case of fever. Patients were regularly assessed for potential AEs and disease-related signs and symptoms. Follow-up including physical examination, tumor assessments and survival data were collected every

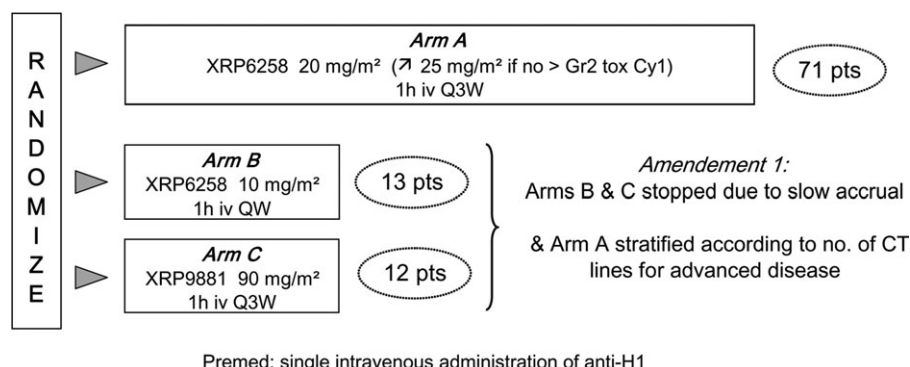


Figure 1. Randomization schedule.

6 weeks for the first 3 months and then every 3 months until the subject's death or until the study cut-off date.

data analysis

Following low recruitment during the first 6 months, the protocol was amended on 21 January 2003. The study consequently became a multicenter, multinational, open-label, single-arm, stratified phase II study in patients with taxane-resistant MBC treated with XRP6258 administered every 3 weeks. Two strata were defined according to the number of lines of taxane-containing treatment previously administered (stratum 1: resistance to an adjuvant/neo-adjuvant or first-line taxane-based regimen for advanced disease versus stratum 2: resistance to a second-line, taxane-based regimen for advanced disease). For each of the strata, a two-stage modified Fleming design was used where accrual was to be stopped if no response was observed after the first 20 per-protocol patients. Within each stratum, if at least one response was observed, 20 additional per-protocol patients were accrued. If at least five responses were observed in the final set of 40 per-protocol patients per stratum, the null hypothesis—that the true response rate was $\leq 5\%$ —was rejected. Overall, at a significance level of 10%, the procedure had a power of 98%.

The primary end point was defined as the objective response rate (ORR), according to RECIST guidelines, achieved by XRP6258 administered every 3 weeks. Secondary efficacy end points were duration of response, time to progression (TTP) and overall survival (OS). They were analyzed using the Kaplan–Meier method [17]. Efficacy was assessed on the treated (all enrolled patients) and the per-protocol population (comprising patients who were eligible for the study and evaluable for response). Duration of response was measured for patients who had complete response (CR) or partial response (PR) as best overall response and calculated as the time from first documentation of CR or PR (whichever status was recorded first) until the first documented progression or death due to any cause. TTP was defined as the time from first infusion to first documented progression or death due to any cause. OS was calculated from the time of first infusion to death, whatever the cause. Where appropriate, 95% confidence intervals (95% CIs) were calculated following the Clopper–Pearson exact method [18].

The safety population included all treated patients. AEs/signs and symptoms of disease observed by the investigator or reported by the patients were recorded and graded according to the National Cancer Institute—Common Toxicity Criteria version 2 whenever possible, otherwise the Medical Dictionary for Regulatory Activities version 6 was used.

results

patients

Of 71 enrolled and treated patients, four were ineligible for the study: two were considered not to be resistant to taxanes, one did not have a histologically confirmed initial breast cancer and one had only one target lesion, in a previously irradiated area. Forty-seven eligible patients were accrued in stratum 1 and 20 in stratum 2. Six patients were not assessable for response due to the administration of concurrent treatments or early discontinuation due to AE or death. The per-protocol population therefore comprised 61 patients. Patient and disease characteristics are summarized in Table 1.

The median age was 53 years and 89% of patients were PS zero to one. All patients had previously received chemotherapy: 1% as adjuvant and 69% and 27% given as first- and second-line for metastatic disease, respectively. A total of seven patients had detectable metastatic disease at presentation and the median DFI for the remaining patients

Table 1. Patient and cancer characteristics

Included patients	N = 71
Age, years	
Median (minimum–maximum)	53 (35–77)
ECOG performance status, N (%)	
0	30 (42)
1	33 (46)
2	7 (10)
Missing	1 (1)
Hormonal status ER and/or PgR, N (%)	
Positive	37 (52)
Unknown	6 (8)
HER2 receptors, N (%)	
Positive	19 (27)
Not done	15 (21)
Disease-free interval, months ^a	
Median (minimum–maximum)	33.3 (1.58–214.01)
Number of organs involved	
1	15 (21)
2	26 (37)
3	14 (20)
4 or more	16 (23)
Main organs involved, N (%)	
Any visceral	53 (75)
Liver	42 (59)
Lymph nodes	33 (46)
Bone	31 (44)
Lung	22 (31)
Breast	16 (23)
Connective soft tissue	11 (15)
Skin	8 (11)
Brain	7 (10)
Prior chemotherapy exposure	
Adjuvant	1 (1)
Advanced	70 (99)
One line ^b	49 (69)
Two lines	19 (27)
Three lines	2 (3)
Prior anthracycline exposure, N (%)	54 (76)
Last taxane exposure, N (%)	71 (100)
Docetaxel	46 (65)
Paclitaxel	25 (35)
More than one line of taxane	7 (10)

^aFor 64 patients with nonmetastatic disease at presentation.

^bIncluding patients with adjuvant chemotherapy with a DFI < 12 months. ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; PgR, progesterone receptor; HER2, human epidermal growth factor receptor 2; DFI, disease-free interval.

was 33.3 months. Hormonal receptor status was positive in 52% of tumors and HER2-positive status was scored in 27% of tumors (Table 1). The majority (75%) of patients had visceral metastatic disease, and 79% had multiple organ involvement (two or more).

exposure to study medication

In total, 345 cycles of XRP6258 were administered, with a median of four cycles (range 1–25 cycles). The median relative

dose intensity was 0.98 (range 0.60–1.14). At least one cycle delay of >3 days was observed in 32% of patients and in 14% of cycles, half of those delays being related to technical or personal reasons. At least one dose reduction was required in 10% of patients and in 2% of cycles. The most frequent reasons for treatment discontinuation were PD (75%), no further benefit expected (13%) and AE (6%).

safety

Treatment emergent grades 3–5 hematological and non-hematological AEs possibly related to study medication are listed by patient and cycle in Table 2. Neutropenia was the most common grade 3/4 hematological AE occurring in 73% of patients and 43% of evaluable cycles. Treatment-related febrile neutropenia or neutropenic infections were observed in 3% and 4% of patients and in <1% of cycles, respectively. Grade 3/4 anemia and thrombocytopenia were rare. Dose escalation up to 25 mg/m² from cycle 2, in selected patients, on the basis of their good tolerance in cycle 1, was feasible in 20 patients (28%) with no evident increase in the overall incidence of subsequent AEs in this group.

Treatment emergent grades 3–5 non-hematological AEs probably or possibly related to study treatment were also rare,

with the most common including: hypersensitivity (4%), fatigue (3%) and hemorrhagic cystitis (3%). No severe AE occurred for nausea, vomiting, neuropathy sensory, myalgia and fluid retention. The most frequent non-hematological AEs at any grade, occurring in >15% of patients, were fatigue (35%), nausea (32%), diarrhea (30%), vomiting (18%), myalgia (17%), neuropathy sensory (17%) and anorexia (15%).

At cut-off, 52 patients had died, with 50 of those deaths considered to be related to disease progression. Two patients died within 30 days of the last on-study treatment: one patient on day 9 of cycle 1, due to shock with respiratory failure, deemed possibly related to study treatment, and one patient on day 21 of cycle 1, of an unknown cause. A total of four patients were withdrawn from the study due to AEs: three patients for grades 1–2 alteration of liver function tests at cycle 1 for one patient and cycle 6 for two patients and one for grade 4 allergic reaction at cycle 2.

efficacy

The investigator-determined ORR was 14% (95% CI 7% to 24%) in the treated patient population (Table 3). Interestingly, two patients achieved a complete response. The median response duration was 7.6 months (range 2.6+ to 18.7+).

Table 2. Grades 3–5 hematological and non-hematological toxic effects possibly or probably related to study treatment

NCI CTC term, N (%)	Patients, N = 71		Cycles, N = 345	
Hematological	All grades	Grade 3/4	All grades	Grade 3/4
Neutropenia ^a	67 (94)	52 (73)	254 (78)	141 (43)
Leukopenia ^b	69 (97)	39 (55)	248 (76)	95 (29)
Anemia ^b	64 (90)	2 (3)	243 (75)	4 (1)
Thrombocytopenia ^b	7 (10)	3 (4)	13 (4)	3 (1)
Neutropenic complications		N = 71		N = 325
All grade 4 neutropenia		35 (49)		67 (21)
Lasting >5 days		19 (27)		26 (8)
Febrile neutropenia		2 (3)		2 (0.6)
Neutropenic infection		3 (4)		3 (1)
Non-hematological	All grades	Grades 3–5	All grades	Grades 3–5
Hypersensitivity reaction	4 (6)	3 (4)	5 (1)	3 (1)
Infection (neutropenic)	3 (4)	3 (4)	3 (1)	3 (1)
Fatigue	25 (35)	2 (3)	68 (20)	3 (1)
Hemorrhagic cystitis	2 (3)	2 (3)	5 (1)	3 (1)
Diarrhea	21 (30)	1 (1)	66 (19)	1 (0.3)
Headache	7 (10)	1 (1)	16 (5)	1 (0.3)
Peripheral edema	6 (8)	1 (1)	16 (5)	1 (0.3)
Infection without neutropenia	3 (4)	1 (1)	4 (1)	1 (0.3)
Arrhythmia supraventricular	1 (1)	1 (1)	1 (0.3)	1 (0.3)
Cyanosis	1 (1) ^c	1 (1) ^c	1 (0.3) ^c	1 (0.3) ^c
Dyspnea	1 (1) ^c	1 (1) ^c	1 (0.3) ^c	1 (0.3) ^c
Incontinence	1 (1)	1 (1)	1 (0.3)	1 (0.3)
Injection site reaction	1 (1)	1 (1)	2 (0.6)	2 (0.6)
Irregular menses	1 (1)	1 (1)	7 (2)	7 (2)
Pleural effusion	1 (1)	1 (1)	2 (0.6)	2 (0.6)
Thromboembolism	1 (1)	1 (1)	1 (0.3)	1 (0.3)

^aN = 325 evaluable cycles.

^bN = 326 evaluable cycles.

^cDeath (grade 5).

NCI CTC, National Cancer Institute Common Toxicity Criteria.

Table 3. Best overall response rate (modified ITT and per-protocol populations)

	Treated population (N = 71)	Per-protocol population (N = 61)
Response, N (%) ^a		
Overall response rate	10 (14)	8 (13)
Complete response	2 (3)	2 (3)
Partial response	8 (11)	6 (10)
No change/stable disease	27 (38)	27 (44)
Progressive disease	29 (41)	26 (43)
Response duration, median (minimum–maximum)	7.6 mo (2.6 ± 18.7+)	7.6 mo (2.6 ± 18.7+)
TTP, median (95% CI)	2.7 months (1.45–4.07)	2.8 months (1.45–4.07)
OS, median (95% CI)	12.3 months (9.49–15.05)	–

^aResponse/disease stabilization confirmed by analyses at least 1 month apart.

TTP, time to progression; OS, overall survival; CI, confidence interval.

In addition to the objective responses, 27 patients (38%) had SD with a median duration of 4.2 months (95% CI 3.71–5.42), including 18 (25%) with tumor stabilization >3 months (from 3.4 to 14.6 months). Eight of these patients had experienced PD as the best overall response to the last taxane treatment. The median TTP was 2.7 months (95% CI 1.45–4.07). At a median follow-up of 20.0 months, the median OS was 12.3 months (95% CI 9.49–15.05). Although numbers were small, no marked difference in response rate was apparent for stratum 1 versus stratum 2 (ORR per-protocol population: 14% versus 12%, respectively).

discussion

Increasingly, taxane- and anthracycline-containing regimens are being used as adjuvant treatments and remain the most efficient systemic treatments and consequently the most commonly used worldwide in the treatment of MBC. After failure of these agents, and particularly in the case of resistance of the tumor to taxanes, the prognosis remains poor. Apart from capecitabine [6, 19], active agents that could be used in subsequent treatment lines are lacking.

XRP6258 appears to be active in docetaxel- or paclitaxel-resistant breast cancer, even when the most stringent criterion of resistance (PD on therapy) was used. The ORR was 14% (95% CI 7% to 24%) in the treated population. In addition, 18 patients (25%) had SD lasting for >3 months (range 3.4–14.6 months). Long-lasting SD may be an indicator of activity, especially in heavily pretreated patients, who did not respond or had responses of short duration to the previous line of chemotherapy. The 14% ORR reported is comparable to that described by Dieras et al. [20] for larotaxel in a similar population. This larotaxel phase II study was conducted in 130 patients with MBC and was designed to assess the efficacy of larotaxel administered every 3 weeks at 90 mg/m² in populations of patients with taxane-resistant and nonresistant disease. The different response rates in these groups (taxane-resistant, 20% versus nonresistant, 42%) highlighted the need to establish a clinical definition of taxane resistance comparable to the model reported for anthracycline breast cancer resistance.

Several drugs have recently been reported to be potentially effective in the treatment of breast cancer patients following the

failure of anthracycline- or taxane-based treatment. These include fluoropyrimidines such as capecitabine [21] and combinations including 5-fluorouracil (5-FU) plus oxaliplatin [22] and 5-FU plus eniluracil [23], but also gemcitabine [24] and vinorelbine [25]. The definitions of taxane resistance across these studies were different and often not restrictive. Only capecitabine was extensively assessed in stringently defined taxane-resistant patients (PD while on therapy). Although no responses were observed with gemcitabine, response rates between 10% and 26% were observed for the other agents/combinations (20% for capecitabine), which are comparable to the 14% rate observed for XRP6258 in this study. Median TTP and median OS times achieved with XRP6258 were also similar to those achieved in these earlier studies. Finally, the semisynthetic epothilone, ixabepilone, has recently been reported to have achieved response rates of 12% in two separate phase II studies in patients with taxane-resistant MBC [26–28], albeit against a background of difficult-to-manage neurotoxicity.

The safety profile of XRP6258 was very favorable when compared with the known safety profile of the marketed taxanes or other compounds under development. No severe AE occurred for nausea, vomiting, neuropathy sensory, myalgia or fluid retention. The most frequent grade 3/4 non-hematological AEs were allergic reaction (4%), fatigue (3%) and diarrhea (1%). The hematological AE profile was also favorable, with rare grade 3/4 anemia and thrombocytopenia. Only grade 3/4 neutropenia was common, occurring in 73% of patients and 43% of cycles. Treatment-related febrile neutropenia occurred rarely. Therefore, the biological mechanism of cytotoxicity coupled with the evidence of activity in taxane-resistant MBC patients and the tolerability of this agent justify further clinical testing.

acknowledgements

We would like to thank the patients who enrolled on this trial and the medical staff who contributed to their care.

conflict of interest

SA is salaried employee of Sanofi Aventis

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Impact, mechanisms, and novel chemotherapy strategies for overcoming resistance to anthracyclines and taxanes in metastatic breast cancer

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Received: 1 April 2008 / Accepted: 2 April 2008 / Published online: 29 April 2008
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Abstract Despite advances in treatment of patients with metastatic breast cancer (MBC), prognosis remains poor and median survival is 2–3 years. Resistance to antineoplastics mediated by many factors, potentially including overexpression of drug efflux proteins or altered β -tubulin isotype expression limits the effectiveness of MBC chemotherapy. Capecitabine, approved for anthracycline- and taxane-resistant MBC, has produced modest responses, highlighting the need for more effective treatments for MBC resistant to multiple chemotherapeutic agents. Agents with potential to reverse drug resistance have not proven effective. Albumin-bound paclitaxel is a formulation that may enhance delivery to tumor tissues. Conversely, ixabepilone, an epothilone analog, has been reported to have lower susceptibility to at least some mechanisms of tumor resistance and clinical activity in resistant/refractory MBC. The topoisomerase-I inhibitor irinotecan also has low cross-resistance with other antineoplastics, and has shown some activity against refractory MBC. Development of new agents and identification of genetic biomarkers in translational studies promise to improve management of patients with resistant/refractory breast cancer.

Keywords Chemotherapy-resistant · Metastatic breast cancer · Ixabepilone · β -Tubulin · P-gp · Drug efflux proteins

Introduction

Breast cancer is the most common cancer of women. Each year, breast cancer is newly diagnosed in more than 1 million patients worldwide; in the United States alone, an estimated 184,450 new cases will be diagnosed in 2008 [1]. Breast cancer causes more than 450,000 deaths each year worldwide with nearly 41,000 deaths estimated to occur from the disease in the United States in 2008 [1]. Approximately 10% of patients with breast cancer have metastatic disease and an additional 10–20% have locally advanced breast cancer [2, 3]. Of the patients diagnosed with early breast cancer, approximately 1 in 3 will develop recurrent or metastatic disease [2]. Options for systemic treatment include chemotherapy, endocrine (hormone) therapy, and biologic agents [2]. Endocrine therapy is often used when the risk of rapid disease progression is low and the disease is not life-threatening [3]. To date, 3 biologic agents, trastuzumab, lapatinib and bevacizumab have been approved for treatment of breast cancer [4, 5]. The chemotherapeutic agents currently available for patients with MBC are outlined in Table 1 [6–8].

Metastatic breast cancer and the impact of resistance

Advances in supportive care and the development of effective systemic therapies have led to consistent improvements in survival for patients with MBC over the last 30 years [9]. However, the prognosis for these patients remains poor—median survival from manifestation of metastases is 2–3 years [9], with a 5-year relative survival rate in the United States of <30% [2]. The recent introduction of novel biological agents might increase survival compared to agents introduced decades ago; however,

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Table 1 Chemotherapy options for patients with metastatic breast cancer [5–7]

Single agents
Anthracyclines (doxorubicin, epirubicin, or pegylated liposomal doxorubicin)
Taxanes (paclitaxel, docetaxel, or albumin-bound paclitaxel)
Capecitabine
Ixabepilone
Combination chemotherapy
FAC/CAF—fluorouracil/doxorubicin/cyclophosphamide
FEC—fluorouracil/epirubicin/cyclophosphamide
AC—doxorubicin/cyclophosphamide
EC—epirubicin/cyclophosphamide
AT—doxorubicin/docetaxel or doxorubicin/paclitaxel
CMF—cyclophosphamide/methotrexate/fluorouracil
XT-Docetaxel/capecitabine
GT—gemcitabine/paclitaxel
Ixabepilone plus capecitabine
Other active drugs
Platinum drugs (cisplatin, carboplatin)
Etoposide
Vinorelbine
Gemcitabine
Mitomycin ^a
Tegafur-uracil ^a
Carmofur ^a

^a Approved for breast cancer treatment in Japan

sufficient follow-up has not yet been completed. Response rates for first-line chemotherapies (alone or in combination) in MBC are approximately 30–70%; however, time to disease progression following treatment with these agents is only 7–10 months [10–12]. Following disease progression with first-line therapies for MBC, the response rate for additional single-agent or combination therapies falls to approximately 20–30%, and the median duration of response is less than 6 months [13].

There is a significant need for new agents that are not susceptible to common tumor-resistance mechanisms. This review discusses mechanisms of resistance to commonly used chemotherapy agents and reports on emerging strategies for the treatment of patients with resistant tumors.

Mechanisms of chemotherapy resistance

Resistance to chemotherapy can be primary (manifesting as tumor insensitivity to initial treatment) or acquired (occurs after initial response to therapy). Both forms of resistance limit the use of chemotherapy to treat cancer [14]. A distinction between acquired resistance and primary resistance

is often made; acquired resistance can be due to the emergence of a subpopulation of intrinsically resistant cells. A number of mechanisms are thought to be involved in the development of tumor resistance to treatment, including changes in β -tubulin isotype expression, β -tubulin mutations, alterations in drug efflux mechanisms and modulation of apoptosis.

One of the most widely studied cellular mechanisms of primary and acquired tumor resistance is alteration in the expression of drug efflux proteins responsible for the removal of many commonly used antineoplastic agents, including anthracyclines and taxanes, from their site of action. In particular, adenosine triphosphate (ATP)-binding cassette (ABC) transporters, a family of transporter proteins, contribute to drug resistance via ATP-dependent cell efflux pumps. This family includes the P-glycoprotein (P-gp) membrane protein encoded by the *MDR1* gene, the multidrug-resistance-associated protein, and the breast cancer resistance protein encoded by the *MXR* gene [15].

In normal tissue, these proteins clear excessive extra- and intracellular concentrations of toxins [16, 17]. Multiple lines of evidence show that ABC transporter genes are overexpressed in human cancers [18], and a number of in vitro studies have demonstrated their role in conferring multidrug resistance [19–21]. A meta-analysis of studies has calculated that approximately 40% of all breast tumors express *MDR1* P-gp, although there was substantial heterogeneity across the individual studies evaluated because of the assay methods used [22].

The anthracyclines and taxanes are some of the many substrates of P-gp and multidrug resistance-associated protein 1 (MRP1) that are likely to be affected by this mechanism of resistance (Table 2). MRP1 also confers resistance to anthracyclines, antifolates, and vinca alkaloids; but not to taxanes, mitoxantrone, or cisplatin (Table 2) [17, 18, 23, 24]. In addition, specific point mutations in the *MXR* gene might confer resistance to mitoxantrone, anthracyclines, methotrexate, and topoiso-merase I (topo I) inhibitors [20, 25].

Table 2 Anticancer drugs known to be substrates of P-glycoprotein (P-gp) and multidrug resistance protein 1 (MRP1)

P-gp	MRP1
Anthracyclines (doxorubicin, daunomycin, epirubicin)	Anthracyclines (doxorubicin, daunomycin, epirubicin)
	Antifolates (methotrexate)
Epipodophyllotoxins (etoposide)	Epipodophyllotoxins (etoposide)
Mitomycin C	
Taxanes (paclitaxel, docetaxel)	
Vinca alkaloids (vincristine, vinblastine)	Vinca alkaloids (vincristine, vinblastine)

Adapted from [16, 17, 22, 23]

Chemotherapeutic agents that target microtubules are also subject to other tumor-resistance mechanisms, such as altered β -tubulin isotype expression, β -tubulin mutations and modifications in microtubule regulatory proteins [26]. For example, the overexpression of the β III-tubulin isoform correlated negatively with paclitaxel response both clinically [27] and preclinically [28] and has been correlated with paclitaxel resistance in many human tumors [27, 28]. However, further investigation is required to establish the full clinical implications of β III-tubulin expression as a marker for response to taxanes.

The precise nature of resistance to capecitabine, an oral prodrug of 5-fluorouracil (5-FU), remains unclear, although several mechanisms of resistance to 5-FU have been proposed. In *in vitro* and *in vivo* preclinical studies, high-level expression of thymidylate synthase, increased activity of deoxyuridine triphosphatase, methylation of the *MLH1* gene, and overexpression of Bcl-2, Bcl-XL, and Mcl-1 proteins have been reported to participate in development of resistance to 5-FU [29].

Overcoming resistance to these mechanisms represents a key therapeutic goal in the development of treatments for patients with metastatic tumors that progress despite use of common chemotherapy regimens. Strategies to circumvent tumor resistance include blockade of resistance mechanisms such as P-gp efflux, and the development of systemic agents with low susceptibility to common resistance mechanisms [30]. Inhibitors of P-gp and MRP1 have been investigated in clinical studies with multiple tumor types. Third-generation P-gp inhibitors such as tariquidar, zosuquidar, and laniquidar are currently under development [31]. Despite evidence that tariquidar is a potent and effective P-gp inhibitor that can be administered with chemotherapy [32], it has shown only limited clinical activity in restoring sensitivity to anthracycline or taxane chemotherapy in chemotherapy-resistant, advanced breast cancer [33].

Treatment options for patients whose tumors are resistant to anthracyclines and taxanes

Until recently, capecitabine was the only US Food and Drug Administration (FDA)-approved chemotherapeutic agent for patients with tumors resistant to both anthracyclines and taxanes in the metastatic setting [34, 35]. Approval was based on a small cohort of 162 patients from a phase II trial of capecitabine twice daily (2510 mg/m²/day) on days 1–14 of a 21-day cycle, in which a 20% overall response rate (ORR) and a median time-to-disease progression (TTP) of 93 days were achieved [36, 37].

Additional phase II studies of capecitabine in anthracycline- and taxane-pretreated and/or -resistant tumors have been conducted (Table 3) [34, 38–40]. Results showed an ORR of 15–29%. Hematologic toxicity and alopecia, which are common with anthracyclines and taxanes, were infrequent; gastrointestinal disorders and hand-foot syndrome were the most common adverse events (AEs). It is important to note that the definitions of *resistance* in the inclusion criteria for these studies differ. For example, in the 1999 study conducted by Blum and colleagues, progression on paclitaxel was a requirement for inclusion; however, it was not necessary to have a taxane as the most recent therapy [36]. Approximately 75% of patients with MBC who develop tumor relapse after anthracyclines and taxanes do not respond to capecitabine treatment, whereas patients who do experience an initial response eventually develop resistance [34, 38–40].

Other agents not approved by the FDA in this setting are used at the physician's discretion to treat patients with tumors resistant to anthracyclines and taxanes. Although many of these agents have been efficacious in small-scale studies, their true clinical impact in large, well-controlled trials remains to be established. Phase II studies have demonstrated activity for oxaliplatin in combination with vinorelbine (ORR 27%; TTP 3.4 months) [41] or with

Table 3 Capecitabine in the treatment of metastatic disease: patients pretreated with anthracyclines and taxanes

Study	Number of patients	Regimen	Pretreatment	ORR (%)	Median duration of response (months)	Median survival (months)	TTP (months)
Blum 1999 [35]	162	2510 mg/m ² /d (Days 1–14)	100% prior taxane, 91% prior anthracycline	20	8.0	12.8	3.1
Blum 2001 [37]	75	2510 mg/m ² /d (Days 1–14)	100% prior taxane, 96% prior anthracycline	26	8.3	12.2	3.2
Reichardt 2003 [38]	136	2500 mg/m ² /d (Days 1–14)	99% prior taxane, 93% prior anthracycline	15	7.5	10.1	3.5
Fumoleau 2004 [33]	126	2500 mg/m ² /d (Days 1–14)	99% prior taxane, 96% prior anthracycline	28	5.9	15.2	4.9
Wist 2004 [39]	48	2500 mg/m ² /d (Days 1–14)	100% prior taxane and anthracycline	29	4.5	9.4	3.6

ORR, overall response rate; TTP, time to progression

fluorouracil (ORR 27%; TTP 4.8 months) [42] in anthracycline- and taxane-pretreated patients. It should be noted that only a proportion of enrollees were classified as having anthracycline- and taxane-resistant tumors. Gemcitabine and platinum combinations are under investigation in patients pretreated with anthracyclines and taxanes [43]; small-scale studies of this regimen in patients with MBC resistant to either anthracyclines or taxanes have reported ORRs of 29–30% and TTP of approximately 7 months [44, 45].

New taxanes that aim to overcome relative resistance to existing members of the class by possibly enhancing intracellular levels have been recently investigated. Both nanoparticle albumin-bound (nab) paclitaxel and larotaxel (XRP-9881 = RPR109881) have been studied as treatments for taxane-refractory MBC (ORR 19–20%) [46, 47]. In a phase III trial, nab-paclitaxel demonstrated a favorable safety profile and had greater efficacy than standard paclitaxel in MBC when administered every 3 weeks [48]. Further, it showed a significantly higher response rate (33% vs. 19%, $P = 0.001$) and longer TTP (5.4 vs. 3.9 months, $P = 0.006$). No severe hypersensitivity reactions occurred despite a shorter administration time and the absence of steroid premedications. Grade 4 neutropenia was significantly lower than standard paclitaxel and febrile neutropenia was uncommon (<2%). Grade 3 sensory neuropathy was more common with nab-paclitaxel than with standard paclitaxel (10% vs. 2%, $P < 0.001$), but it was easily managed and improved rapidly [47]. Nab-paclitaxel and larotaxel are currently undergoing trials in combination with capecitabine and other agents for management of breast cancer [49–54].

Potential options for patients with tumors refractory to anthracyclines, taxanes, and capecitabine

There are few treatment options for patients showing resistance to anthracyclines, taxanes, and capecitabine (triple-refractory). Although “targeted” therapies continue to be investigated, there are none which at this time have been demonstrated to improve patient outcome in randomized trials. Thus, another logical option has been to continue investigation of novel chemotherapies, which in essence are also targeted drugs against apoptosis. Chemotherapeutic agents under investigation in this patient population include the antifolate pemetrexed, the topo-I inhibitor irinotecan, and the epothilones, a novel class of antineoplastic agents, and their analogs.

Pemetrexed has been investigated in a recent study that enrolled 80 patients with advanced breast cancer previously treated with an anthracycline, a taxane, and capecitabine; but the inclusion criteria did not require tumors to be refractory to all 3 agents [55]. Despite a stable

disease (SD) rate of 36%, the reported ORR was only 8%. Grade 3 toxicities consisted primarily of neutropenia (29%) and leukopenia (21%) [55].

Oral irinotecan has been evaluated in a phase II study in patients with MBC after failure with an anthracycline, a taxane, and capecitabine [56]. The definition of failure of prior anthracycline, taxane, and capecitabine in this trial includes progression during or following treatment, lack of response after ≥ 4 cycles, or significant treatment-related toxicity [56]. Consequently, not all enrollees can be classified as having triple-refractory disease. In many cases, resistance to a prior agent was not clearly documented before enrollment; however, there was encouraging activity (22% ORR; 41% SD) [55]. A second phase II study evaluated the efficacy and tolerability of 2 irinotecan schedules [57]. With weekly dosing, Grade 3/4 drug-related AEs with $\geq 10\%$ incidence included neutropenia (29%) and diarrhea (17%). Neutropenia (36%), vomiting (20%), dyspnea (18%), nausea (16%), and diarrhea (12%) were seen with every 3-week dosing [57]. Irinotecan has a distinct mechanism of action and limited cross resistance with common therapeutic agents, which might have contributed to its activity in this population [57]. However, further development of this drug does not appear to be occurring.

However, because of the definitions of *resistance* employed in these studies, results are not always clearly related to triple-refractory tumors. For example, patients could have discontinued prior treatment because of significant toxicity—not true clinical resistance. A notable exception to this general approach is a study conducted by Perez and colleagues that evaluated the novel epothilone B analog ixabepilone as monotherapy in patients with triple-refractory metastatic disease [58]. Resistance criteria in this study were strict: disease progression within 8 weeks of the last dose of an anthracycline, a taxane, or capecitabine in the metastatic setting, or within 6 months of the last dose of adjuvant or neoadjuvant anthracycline or taxane. Data for this trial, detailed below, are notable because tumors were truly refractory to 3 approved antineoplastic agents (anthracyclines, taxane, and capecitabine).

The epothilones

The natural epothilones and their analogs are a new class of antineoplastics, derived from the myxobacterium *Sorangium cellulosum* that induce tumor cell apoptosis by stabilizing microtubules involved in mitosis [59, 60]. Epothilones in development include patupilone (EPO906; natural epothilone B), KOS-1584 (9,10-didehydroepothilone D), and the fully synthetic analogs ABJ879 (C20-desmethyl-C20-methylsulfanyl-Epo B) and ZK-EPO [59, 61].

Patupilone has shown cytotoxicity to multidrug-resistant cell lines that overexpress the drug efflux protein P-gp [59]. In addition, patupilone retains activity against ovarian cancer cells with β -tubulin mutations that render them resistant to paclitaxel [62, 63]. Two phase I trials of patupilone with different schedules have been reported in breast cancer, as well as 2 phase I trials in combination with carboplatin and a phase I trial in combination with capecitabine [64]. A second epothilone analog, ZK-EPO, is in phase II trials. KOS-1584 is a novel epothilone analog with favorable pharmacokinetic properties that has entered phase II trials [65].

Ixabepilone

Ixabepilone is the first epothilone to gain approval by the FDA based on completed phase II/III trials in MBC. Ixabepilone is a poor substrate for efflux proteins and has demonstrated low susceptibility to multiple tumor-resistance mechanisms. The compound has shown activity in tumor cell lines that overexpress β -tubulin [66], a mechanism potentially important to the development of clinical resistance to taxanes. Ixabepilone has been investigated in a phase II trial as a single agent in heavily pretreated MBC patients with triple-refractory disease that had strict criteria for resistance to prior therapy [58]. Furthermore, patients were heavily pretreated and had extensive metastatic disease, including visceral involvement. Results for 113 evaluable patients revealed an independent radiology facility (IRF)-assessed ORR of 11.5% with ixabepilone; SD was achieved by 50% of treated patients with a duration ≥ 6 months in 14.3% of patients [58]. AEs were manageable; the most common non-hematologic Grade 3/4 events were peripheral sensory neuropathy (14%), fatigue/asthenia (14%), and myalgia/arthralgia (8%). Results of another phase II study in patients with MBC resistant to taxanes showed that ixabepilone has clear antitumor activity in these patients [67]. Resistance criteria required tumor progression on or within 4 months of taxane therapy (or within 6 months, if adjuvant taxane only) and a taxane as the last regimen. Consequently, patients had tumors that were highly resistant to antimicrotubule agents. The ORR was 12%, and 41% of patients achieved SD [67]. Studies of other agents in the refractory breast cancer population help to put the data with ixabepilone in perspective; Blum and colleagues evaluated capecitabine in patients with progressive disease after treatment with paclitaxel. This trial reported a 20% ORR and a 40% SD rate [36]. In another study conducted by Valero and colleagues, docetaxel was administered to patients with prior progression on paclitaxel [68]. An 18.1% ORR was reported with 32% of patients achieving SD [68]. Because not all studies

required that a taxane be the most recent therapy, it is possible that these findings represent outcomes in a less refractory population compared with the ixabepilone studies.

Ixabepilone in combination with capecitabine has also been evaluated in two large phase III MBC trials comparing efficacy and safety of the combination regimen vs capecitabine alone. Results of one of these studies showed that ixabepilone plus capecitabine was superior to capecitabine across endpoints, and achieved a significant benefit across subgroups [69], including patients with ER/PR/HER2-negative and HER2-positive disease. In the total population, ixabepilone plus capecitabine demonstrated improved efficacy versus capecitabine monotherapy with significant prolongation of median PFS (5.8 months vs. 4.2 months; $P = 0.0003$) and increased response rate (34.7% vs. 14.3%; $P < 0.0001$). Ixabepilone had a manageable safety profile in this heavily pretreated population. Grade 3/4 adverse events (ixabepilone plus capecitabine, capecitabine), included peripheral neuropathy (23%, 0%), hand-foot syndrome (18%, 17%), and fatigue (9%, 3%). Neuropathy was cumulative and reversible in most patients. Grade 3/4 neutropenia was reported in 32% and 36%, respectively, in the combination arm vs 9% and 2% in the monotherapy arm; febrile neutropenia was 5% with ixabepilone plus capecitabine; 3 patients (1%) in the ixabepilone plus capecitabine arm reported grade 5 febrile neutropenia [69].

Conclusions

Optimal management of MBC remains a significant therapeutic challenge. Due to frequent occurrence of primary or acquired drug-resistant disease, development of therapeutic options able to overcome such resistance is of paramount importance. Capecitabine was until recently the only approved treatment for tumors that develop resistance to both anthracyclines and taxanes. However, in the majority of these patients ($\sim 75\%$), tumors fail to respond to capecitabine and resistance inevitably develops, resulting in triple-refractory disease that had no approved treatment options. The epothilone B analog ixabepilone has demonstrated efficacy in drug-resistant MBC and was recently approved as mono- or combination therapy by the FDA for the treatment of locally advanced or metastatic resistant/refractory breast cancer. This advance is an example of the progress being made in finding new strategies to manage patients with progressing or relapsing disease refractory to anthracyclines, taxanes and/or capecitabine, but additional work is needed to identify biological predictors of resistance so that novel strategies may be identified.

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